Review Article

Does low-dose computed tomography screening improve lung cancer-related outcomes?—a systematic review

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Abstract: Screening with low-dose computed tomography (LDCT) can potentially decrease the mortality rate of lung cancer by detecting tumors at earlier stages. Although a number of guidelines exist on the implementation of screening and the management of screening-detected lesions, the field has progressed since those were written in terms of the clinical data now available and the greater range of surgical options now on offer to patients. This systematic review aims to provide an updated assessment of how LDCT screening may impact lung cancer-related outcomes in light of such recent data and surgical progress. A systematic literature search was conducted to identify articles focused on the use of LDCT to screen for primary non-small cell lung cancer in asymptomatic individuals. Of 2,880 articles identified, high quality papers reporting the results of 27 major studies were selected for in-depth analysis—including 17 observational studies (15 prospective and 2 retrospective), and 11 randomised-controlled trials. LDCT screening detected lung cancer in 0–8.2% of asymptomatic adults subject. These rates were demonstrated in most studies to be significantly higher than the lung cancer detection rate with no screening. Invasive procedures for benign lesions were performed in 0.07–1.9% of LDCT-screened subjects. Most LDCT screening-detected lung cancers presented in stage I, and 52–100% of patients with LDCT-detected lung cancer received surgery. Two large randomized-controlled trials showed that LDCT screening was associated with a 20.0% reduction in mortality when compared to chest X-ray (CXR) screening, and a 26% reduction in mortality when compared to no screening. LDCT screening is associated with: higher rates of lung cancer detection; diagnosis of lung cancer at an earlier stage; greater likelihood of surgical therapy being given; and lower mortality from lung cancer. The rate of 'unnecessary' interventions as a result of LDCT screening is low.

Keywords: Low-dose CT (LDCT); lung cancer; screening; survival; outcomes

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Introduction

Lung cancer is the second commonest cancer and leading cause of cancer-related deaths in Hong Kong, killing 3,780 patients in 2016 (1). The high mortality rate of lung cancer can be attributed to its generally late presentation, with around 69% of patients presenting at stage III or IV disease and therefore not amenable to surgical treatment (2). It has been postulated that screening can improve lung cancer survival by detection of tumours while they are still in resectable early stages. However, over the years, methods such as sputum cytology and chest X-ray (CXR) have been shown to be inadequately sensitive for screening purposes, while conventional computed tomography (CT) confers an unacceptably high radiation dose (3).

The advent of low-dose CT (LDCT) technology has made it possible to obtain high-quality images with a low

radiation exposure (4), and recent studies have investigated the use of LDCT thorax scans to screen for lung cancer with some encouraging results. Based on multiple early trials conducted in the west, the United States and Canada have published guidelines on LDCT lung cancer screening programs for high-risk populations a number of years ago (5,6).

One of the upshots of lung cancer screening is that potentially smaller lesions may be detected and be amenable to the latest forms of minimally invasive thoracic surgery (7). Video-assisted thoracic surgery (VATS) has evolved in recent years, and can now be performed via Uniportal approach, promising less surgical access trauma and better patient recovery than ever before (8,9). In addition, sublobar resection has now been demonstrated to offer equally effective therapy for smaller lung cancers, such as those typically identified by screening (7,10). The advent of LDCT screening appears to have arrived at the optimal time to take advantage of these latest thoracic surgical advances.

As more randomised-controlled trials are emerging in recent years from different countries, including some in Asia, an updated literature review is now due in order to update and refine screening practices (11). The primary objective of this systematic review was to provide an updated assessment of how LDCT screening may impact lung cancer-related outcomes. The secondary objective was to explore the relevance of the existing literature to populations in Asia, where VATS and sublobar resections are especially commonly practiced (12).

Methodology

Search method

Between November and December 2018, literature searches were conducted through the Ovid search engine in the PubMed and the MEDLINE database for original clinical studies, using the MeSH terms (Tomography, X-Ray Computed) AND (lung or pulmonary or non-small cell) AND (cancer or ca or neoplasm or malignancy or tumour) AND (screen or early detection or early diagnosis). The inclusion criteria included retrospective or prospective, and observational or randomised-controlled trials (with an alternative screening protocol or standard care as control) of any sample size, which utilised LDCT thorax scans to screen for primary, non-small cell lung cancer in asymptomatic individuals and published data in English on any combination of outcomes including lung cancer detection rate, invasive intervention rate, false positive rate of CT scans and invasive interventions, staging, and resection rate of diagnosed cancers, and mortality rate. The exclusion criteria included articles that were not published in English or Science Citation Index (SCI) peer-reviewed journals. Titles and abstracts were assessed for relevance to the primary objective, and the resulting full papers were read in their entirety for adherence to the inclusion criteria.

Data extraction and outcome measures

Each study's authors, publication year and methods were extracted. The outcome measures examined were the lung cancer detection rate, LDCT false positive rate, rate of unnecessary invasive procedures, staging distribution of LDCT-detected lung cancers, resection rate of LDCT-detected lung cancers, and lung cancer-related mortality.

Lung cancer detection rate was defined as the percentage of screened cases detected to have lung cancer. LDCT false positive rate was defined as the percentage of LDCT scan-positive subjects referred for further follow-up, including specialist appointments, repeat scan or more invasive procedures, who ultimately had benign lesions. The rate of unnecessary invasive procedures was defined as the percentage of screened subjects who received invasive procedures, including bronchoscopy, tissue biopsy or surgical resection, who ultimately had benign lesions. Staging distribution of LDCT-detected lung cancers was defined according to the tumour, node, and metastasis classification of lung cancer in the sixth edition of the Cancer Staging Manual by the American Joint Committee on Cancer. Lung cancer-related mortality was defined as the percentage of lung cancer patients who ultimately died from lung cancer-related mortality.

For trials with multiple published articles, the most updated data was used. *Figure 1* displays the search methodology.

Results

The initial literature search yielded 2,880 articles, 1,028 of which were duplications. Irrelevant studies, non-clinical trials and reports with no measured outcomes were excluded based on the studies' titles and abstracts, resulting in 53 articles which were read in their entirety. After excluding articles that were not in English or did not report on this

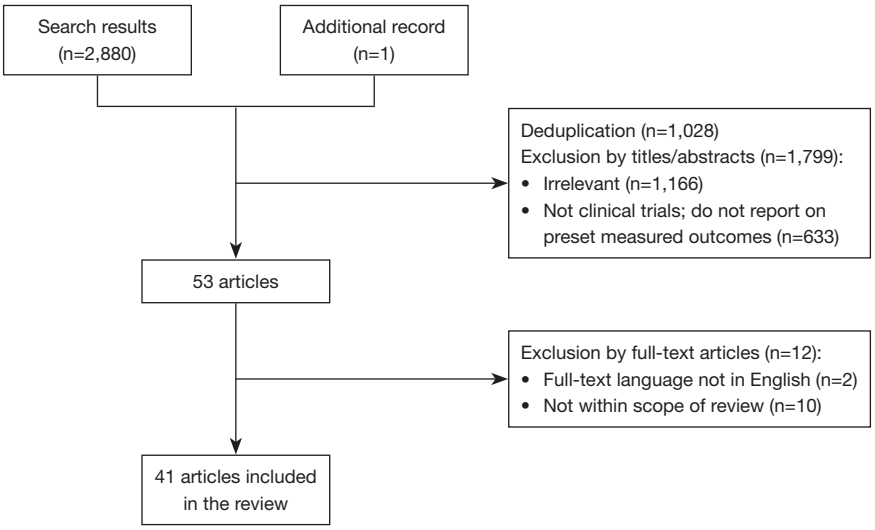

Figure 1 Search methodology.

review's outcome measures, 40 articles reporting (2,13-36) on 27 studies (37-51), and one additional press release with the most updated results of one of the largest trials to date (52), were included in this review. Among the reviewed studies, 17 were observational studies (15 prospective and 2 retrospective) (13-31,53), and 11 were randomised-controlled trials (RCTs) (32-52). Among the RCTs, 10 had published comparative data, three of which compared LDCT screening with CXR screening (32-35) and seven of which compared LDCT screening with no screening (36-45,51,52).

Study designs and baseline characteristics

The study design and baseline characteristics of each study are presented in *Table 1*. In general, the observational studies included both male and female subjects older than 40 years old (median ages 50–67 years old) with at least 10 pack-years (median pack-years 20–53.6) of cigarette smoking history, had screening frequencies ranging from a one-off screening to five annual screenings, and recruited sample sizes of 154 to 3,167 subjects (2,13-31). Most of the RCTs included more males than females subjects, 50- to 75-year-old (median ages 55–67 years old) with at least 20 pack-years (median pack-years 10–54), had screening frequencies ranging from 1 to 5 annual screens, and recruited sample sizes of 654 to 53,454 subjects (32-51). The two largest RCTs (NLST and NELSON) have a combined sample size of more than twice the combined sample size of the rest of the RCTs (35,47).

Lung cancer detection rate

Studies that performed one, two, three, four and five LDCT screenings detected lung cancer in 0–2.7%, 0.8–2.4%, 0.9–4.0%, 3.1–4.2% and 2.4–8.2% of their participants respectively. CXR detected lung cancer in 0.3–3.5% of their participants as reported by 3 RCTs, and 0.3–6.0% of individuals who received no screening were eventually diagnosed with lung cancer as reported by 6 RCTs.

The lung cancer detection rate between LDCT versus CXR screening was compared in one RCT, which showed a significantly higher lung cancer detection rate by LDCT screening (RR 1.03–1.23). The lung cancer detection rate in the LDCT screening versus no screening groups was compared in four RCTs, three of which showed a significantly higher lung cancer detection rate by LDCT ($P \leq 0.001$ to 0.042) while one showed no significant difference (RR 95% CI, 0.7–1.3) (*Table 2*).

Rates of false positive (FP) and unnecessary invasive procedures

The FP rates were reported to be 59.4–100% for LDCT according to 14 observational studies and nine RCTs, and 92.3–94.3% for CXR according to three RCTs (*Table 2*).

The percentage of total screened subjects who ultimately received unnecessary invasive procedures for benign lesions

Table 1 Design and characteristics of reviewed studies

Study (years published; region)	Included subjects	Screenings/ subject	Sample size	% male	Median age (years old)	Median pack-years
Observational studies						
Prospective						
Chong *et al.* (2005; Korea) (13)	≥45 years old	1	6,406	86	55	25.6
Crucitti *et al.* (2015; Italy) (14)	≥55 years old & 1 RF for lung cancer	1	1,500	62	61.8	41.8
dos Santos *et al.* (2016; Brazil) (15)	55–74 years old & ≥30 pack-years	1	790	49.9	61.9	53.6
Henschke *et al.* (2001; US) (16)	≥60 years old & ≥10 pack-years	1	1,000	54	67	45
I-ELCAP investigators (2006; international) (17)	≥40 years old & 1 RF for lung cancer	2 annual	31,567	–	61	30
Lam *et al.* (2015; US) (18)	≥50 years old & ≥20 pack-years	1	154	41.6	64.4	45.4
Luo *et al.* (2017; China) (19)	50–80 years old & 1 RF for lung cancer	1	11,332	63	63.5	20–40
McKee *et al.* (2013; US) (20)	55–74 years old & >20 pack-years; >50 years old, 1 RF & ≥30 pack-years	1	500	51.2	62.5	47.7
Menezes *et al.* (2010; Canada) (21)	≥50 years old & ≥10 pack-years	2 annual	3,352	46	60	30
Nawa *et al.* (2002, 2012; Japan) (22,23)	≥50 years old, 62.1% (ex-)smokers	2 annual	7,956	79.4	55–59	–
NY-ELCAP investigators (2007; US) (24)	≥60 years old & ≥10 pack-years	3 annual	6,295	48.8	66	40
Sanchez-Salcedo *et al.* (2015; Spain) (25)	≥40 years old & ≥10 pack-years	3 annual	2,989	73	55	32
Swensen *et al.* (2003, 2005; US) (26,27)	≥50 years old & ≥20 pack-years	5 annual	1,520	52	59	45
Toyoda *et al.* (2008; Japan) (28)	≥40 years old, 87.5% (ex-)smokers	3 annual	4,689	59	50–59	–
Veronesi *et al.* (2008, 2014; Italy) (29,30)	≥50 years old & ≥20 pack-years	5 annual	5,203	57	57	44
Retrospective						
Ahmed *et al.* (2018; US) (31)	Asymptomatic adults	1	272	50	64	42
Chen *et al.* (2016; Taiwan) (2)	Asymptomatic adults	1	3,339	52.3	48	–
Randomised-controlled trials	Inclusion criteria	(follow-up)	(LDCT; control)			
LDCT screening versus CXR screening						
Depiscan (2007; France) (32)	50–75 years old & ≥15 pack-years, quit for <15 years	3 annual (0 year)	765 (385; 380)	71	56	34.9
LSS (2004, 2005; US) (33,34)	55–74 years old & ≥30 pack-years, quit for <10 years	2 annual (0 year)	3,318 (1,660; 1,658)	59	55-64	54
NLST (2011; US) (35)	55–74 years old & ≥30 pack-years, quit for ≤15 years	3 annual (6.5 years)	53,454 (26,722; 26,732)	59	61	48

Table 1 (*continued*)

Table 1 (*continued*)

Study (years published; region)	Included subjects	Screenings/ subject	Sample size	% male	Median age (years old)	Median pack-years
LDCT screening versus no screening						
DANTE (2009, 2015; Italy) (36,37)	60–74 years old & ≥20 pack-years, quit for <10 years	5 annual (8 years)	2,450 (1,264; 1,186)	100	64.3	47.3
DLCST (2009, 2012, 2016; Denmark) (38-40)	50–70 years old & ≥20 pack-years, quit for <10 years	5 annual (10 years)	4,104 (2052; 2,052)	55.8	58	36
ITALUNG (2013, 2017; Italy) (41,42)	55–69 years old & ≥20 pack-years, quit for ≤10 years	4 annual (6 years)	3,206 (1,613; 1,593)	64	60.9	40
LUSI (2012, 2015; Germany) (43,44)	50–69 years old & ≥15 cigarettes/ day for ≥25 years; ≥10 cigarettes/ day for ≥30 years, quit for <10 years	4 annual (3 years)	4,052 (2,029; 2,023)	64.7	58	36
MILD (2012; Italy) (45)	≥49 years old & ≥20 pack-years, quit for <10 years	3 biennial/ 5 annual (5 years)	4,099 (1,186 CT-B, 1,190 CT-A; 1,723 control)	CT-B: 69; CT-A: 68	CT-B: 58; CT-A: 57	CT-B: 39; CT-A: 39
NELSON (2009, 2013, 2016, 2017, 2018; Netherlands) (46-49,52)	50–75 years old & ≥15 cigarettes/ day for ≥25 years; ≥10 cigarettes/ day for ≥30 years, quit for <10 years	4: 1, 2 and 2.5 years apart (0 year)	15,822 (7,915; 7,907)	84	59	42
UKLS (2016; UK) (50)	50–75 years old & LLPv2 risk ≥5%	1 (0 year)	4,055 (2,028; 2,027)	75.4	67	–
Yang *et al.* (2018; China) (51)	45–70 years old & 1 RF for lung cancer	3 biennial (0 year)	6,657 (3,512; 3,145)	46.8	59.8	0–20

LDCT, low-dose computed tomography; CXR, chest X-ray; US, United States; UK, United Kingdom; RF, risk factor; CT-A, computed tomography group A; CT-B, computed tomography group B; LLPv2, Liverpool Lung Project v2.

was 0.07–1.9% for LDCT according to 11 observational studies and nine RCTs, 0.06–0.09% for CXR according to two RCTs, and 0.42% for no screening according to one RCT (*Table 2*).

Stages of diagnosed lung cancers

LDCT-detected lung cancers presented 33.3–96.1% at stage I, 0–50.0% at stage II, 0–50.0% at stage III, and 0–36% at stage IV, as reported by 14 observational studies and all 11 RCTs. CXR-detected lung cancers presented 30.7–100.0% at stage I, 0–7.9% at stage II, 0–25% at stage III, and 0–35.6% at stage IV, as reported by three RCTs. Lung cancers diagnosed in subjects receiving no screening presented 9.4–22.2% at stage I, 3.8–30.0% at stage II, 10.0–17.0% at stage III, and 40.0–60.4% at stage IV, as reported by five RCTs (*Table 3*). *Figure 2* displays the staging proportions from RCTs with comparative data.

The staging distribution of lung cancers detected by the LDCT versus CXR screening was compared in one RCT, which showed no significant difference (P=0.8). The staging distribution of lung cancers diagnosed in the LDCT screening versus no screening groups was compared in four RCTs, of which three showed a significantly higher proportion of stage I disease detected in the LDCT group (P<0.0001 to <0.001), one showed no significant difference in proportion of stage IV disease (P=0.28), and one showed no significant difference in proportion of advanced disease (Union for International Cancer Control's stage II or above; P=0.25) (*Table 3*).

Resection rates of diagnosed lung cancers

The proportion of lung cancers that was resected was 52–100% for LDCT-detected subjects as reported by 11 observational studies and four RCTs, 44.1% for CXR-detected subjects as reported by one RCT, and 28–29.1% for subjects who received no screening as reported by two RCTs (*Table 3*). The lung cancer resection rate in the LDCT screening versus no screening groups was compared

Table 2 Rates of lung cancers, false positives and unnecessary interventions

Study	Lung cancers diagnosed (n, % of total)	LDCT false positives (% of scan positives)	Unnecessary interventions (% of screened)
Observational studies			
Chong *et al.* (13)	23, 0.36%	99.0%	–
Crucitti *et al.* (14)	24, 1.6%	95.3%	0.33%
dos Santos *et al.* (15)	10, 1.3%	96.8%	1.90%
Henschke *et al.* (16)	27, 2.7%	88.3%	0.10%
I-ELCAP (17)	484, 1.53%	–	–
Lam *et al.* (18)	0, 0%	100%	1.30%
Luo *et al.* (19)	27, 0.24%	86.2%	0.12%
McKee *et al.* (20)	3, 0.6%	97.6%	–
Menezes *et al.* (21)	65, 1.9%	89.2%	0.63%
Nawa *et al.* (22,23)	210, 0.83%	98.7%	0.19%
NY-ELCAP (24)	125, 2.00%	90.1%	0.26%
Sanchez-Salcedo *et al.* (25)	53, 1.77%	–	–
Swensen *et al.* (26,27)	66, 4.34%	96.0%	0.53%
Toyoda *et al.* (28)	40, 0.85%	89.6%	–
Veronesi *et al.* (29,30)	175, 3.4%	–	0.56%
Ahmed *et al.* (31)	6, 2.2%	88.7%	–
Chen *et al.* (2)	30, 0.9%	97.7%	0.30%
Randomised-controlled trials			
Depiscan (32)	CT: 8, 2.4%; XR: 1, 0.3%	CT: 90.0%; XR: 94.3%	–
LSS (33,34)	CT: 40, 2.41%; XR: 20, 1.21%	CT: 93.0%; XR: 92.3%	CT: 0.60%; XR: 0.06%
NLST (35)	CT: 1060, 3.97%; XR: 941, 3.52%	CT: 95%; XR: 93%	CT: 0.25%; XR: 0.09%
DANTE (36,37)	CT: 104, 8.23%; NS: 72, 5.98%	86.0%	CT: 1.34%; NS: 0.42%
DLCST (38-40)	CT: 100, 4.87%; NS: 53, 2.58%	88.7%	CT: 0.07%
ITALUNG (41,42)	CT: 67, 4.15%; NS: 71, 4.46%	96.6%	CT: 0.62%
LUSI (43,44)	CT: 62, 3.06%; NS: 32, 1.58%	–	CT: 1.13%
MILD (45)	Biennial CT: 20, 1.69%; annual CT: 29, 2.44%; NS: 20, 1.16%	–	CT: 0.17%
NELSON (46-49,52)	CT: 255, 3.2%	59.4%	–
UKLS (50)	CT: 42, 2.1%	92.4%	CT: 0.20%
Yang *et al.* (baseline) (51)	CT: 51, 1.48%; NS: 10, 0.32%	93.7%	CT: 0.26%

LDCT, low-dose computed tomography; XR, X-ray; NS, no screening.

Table 3 Stages and rates of resection of diagnosed lung cancers

Study	Staging (% of total diagnosed cancers)				Cancers resected
	Stage I	Stage II	Stage III	Stage IV	
Observational studies					
Chong *et al.* (13)	56.5%	4.3%	21.7%	8.7%	65.2%
Crucitti *et al.* (14)	88%	12%	0%	0%	–
dos Santos *et al.* (15)	80%	0%	10%	10%	90%
Henschke *et al.* (16)	85%	–	–	–	96%
I-ELCAP (17)	85.1%	–	–	–	84.9%
Lam *et al.* (18)	–	–	–	–	–
Luo *et al.* (19)	81.48%	–	–	–	–
McKee *et al.* (20)	66.7%	33.3%	0%	0%	–
Menezes *et al.* (21)	71.1%	6.8%	8.5%	8.5%	73.8%
Nawa *et al.* (22,23)	91.0%	4.76%	2.86%	1.43%	96.7%
NY-ELCAP (24)	72.7%	–	–	–	80.2%
Sanchez-Salcedo *et al.* (25)	66.7%	8.3%	10.0%	6.7%	–
Swensen *et al.* (26,27)	60.0%	12.3%	12.3%	3.1%	77.5%
Toyoda *et al.* (28)	–	–	–	–	–
Veronesi *et al.* (29,30)	–(78% N0M0)	–	–	–	87.4%
Ahmed *et al.* (31)	33.3%	50.0%	16.7%	0%	83.3%
Chen *et al.* (2)	53.3% (40% AIS)	3.3%	3.3%	0%	100.0%
Randomised-controlled trials					
Depiscan (32)	CT: 37.5%; XR: 100.0%	CT: 0%; XR: 0%	CT: 50.0%; XR: 0%	CT: 12.5%; XR: 0%	–
LSS (33,34)	CT: 48%; XR: 40%	CT: 8%; XR: 5%	CT: 28%; XR: 25%	CT: 13%; XR: 20%	–
NLST (35)	CT: 49.1%; XR: 30.7%	CT: 6.9%; XR: 7.9%	CT: 20.8%; XR: 24.5%	CT: 21.3%; XR: 35.6%	CT: 60.6%; XR: 44.1%
DANTE (36,37)	CT: 45.2%; NS: 22.2%	CT: 6.7%; NS: 6.9%	CT: 16.3%; NS: 16.7%	CT: 25.0%; NS: 45.8%	CT: 54.8%; NS: 29.1%
DLCST (38-40)	CT: 50.0%; NS: 15.1%	CT: 4.0%; NS: 3.8%	CT: 23.0%; NS: 17.0%	CT: 23.0%; NS: 60.4%	–
ITALUNG (41,42)	CT: 36%; NS: 11%	CT: 7%; NS: 7%	CT: 13%; NS: 11%	CT: 36%; NS: 49%	CT: 52%; NS: 28%
LUSI (43,44)	CT: 67.7%; NS: 9.4%	CT: 8.1%; NS: –	CT: 9.7%; NS: –	CT: 4.8%; NS: –	–
MILD (45)	CT-A: 62.0%; CT-B: 70.0%	CT-A: 6.8%; CT-B: 5.0%	CT-A: 13.8%; CT-B: 10.0%	CT-A: 17.2%; CT-B: 15.0%	–
NELSON (46-49,52)	CT: 69%	CT: 8.2%	CT: 16.5%	CT: 6.3%	CT: 67.7%; NS: 24.5%
UKLS (50)	CT: 66.7%	CT: 19.0%	CT: 7.1%	CT: 7.1%	CT: 83.3%
Yang *et al.* (baseline) (51)	CT: 96.1%; NS: 20.0%	CT: 2.0%; NS: 30.0%	CT: 2.0%; NS: 10.0%	CT: 0%; NS: 40.0%	–

Percentages don't add up because some papers did not provide data on the stages of lung cancers diagnosed. AIS, adenocarcinoma in-situ; CT, computed tomography; NS, no screening.

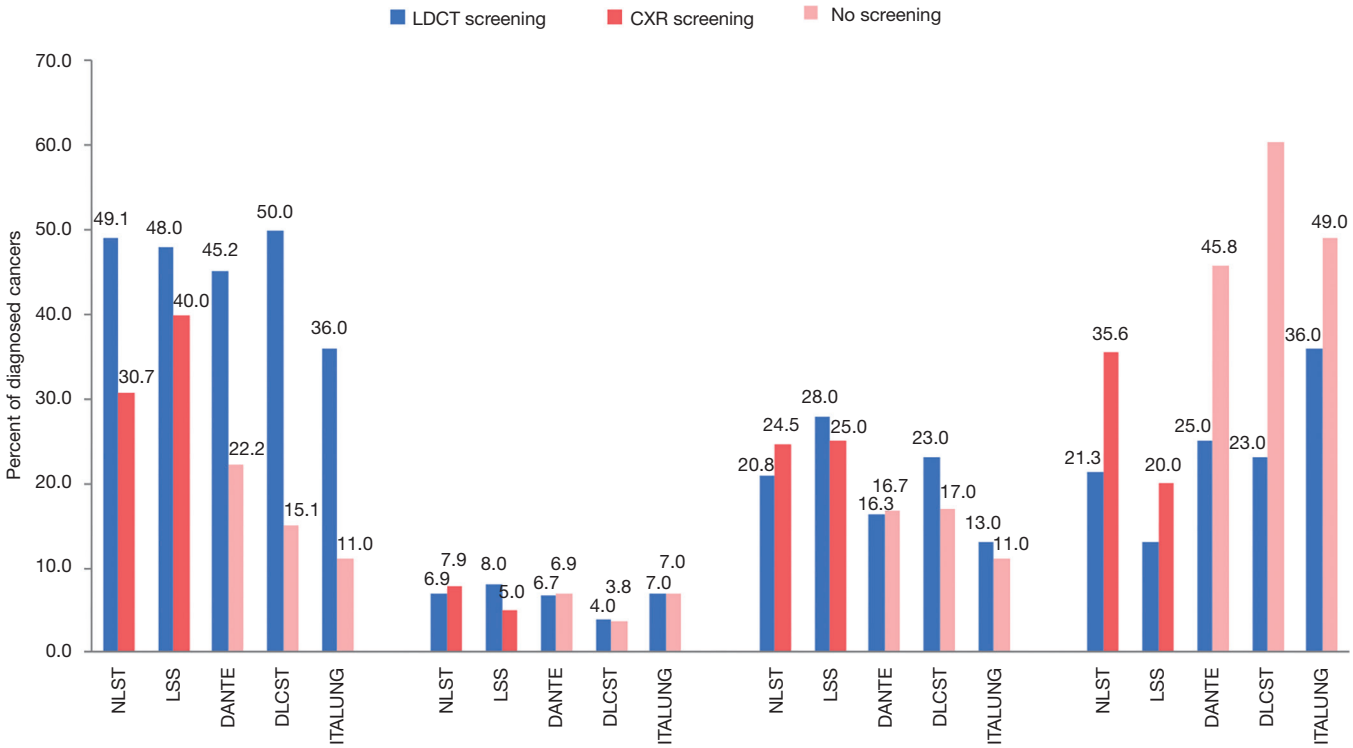

Figure 2 Staging data reported by randomised-controlled trials. LDCT, low-dose computed tomography; CXR, chest X-ray.

in three RCTs, all of which showed a significantly higher lung cancer resection rate in the LDCT group (P≤0.003).

Lung cancer-related mortality

Lung cancer-related mortality in LDCT versus CXR screening groups was compared in one RCT, which showed a significant 20.0% reduction in mortality by LDCT screening compared to CXR screening (P=0.004). Lung cancer-related mortality in the LDCT versus no screening groups was compared in five RCTs, of which one showed a significant 26% reduction in mortality by LDCT screening (95% CI, 9–41%, dataset not yet available and not shown in *Figure 3*) and four showed no significant difference (P>0.05) (*Figure 3*).

Discussion

This review of current literature shows that LDCT screening is successful in detecting a high number of lung cancers among a high-risk population, especially when compared to CXR or no screening. While all studies found a high LDCT false positive rate of at least 59.4%, most of these false positive scans did not necessitate any extra procedures, resulting in a low 0.07–1.9% rate of unnecessary interventions for benign lesions. The lung cancers detected by LDCT screening tend to be in their earlier stages, and the proportion of stage I cancers among LDCT-screened subjects is found by most RCTs to be higher than among non-screened subjects. The proportion of LDCT-detected lung cancers amenable to treatment by resection is above 50% for all studies, which is significantly higher than cancers diagnosed in individuals with no screening. The lung cancer-related mortality may be significantly decreased by LDCT screening when compared to CXR or no screening, but this effect was only seen in two of the six RCTs with comparative data (*Figure 3*).

LDCT has the ability to identify pulmonary lesions as small as 5 mm or below, well before the lesions can cause any clinical symptoms (54). It is therefore not surprising that LDCT leads to a higher detection rate of lung cancers, particularly of earlier-stage lung cancers, as concluded by this review. Lung cancers diagnosed at earlier stages are associated with a higher survival compared to

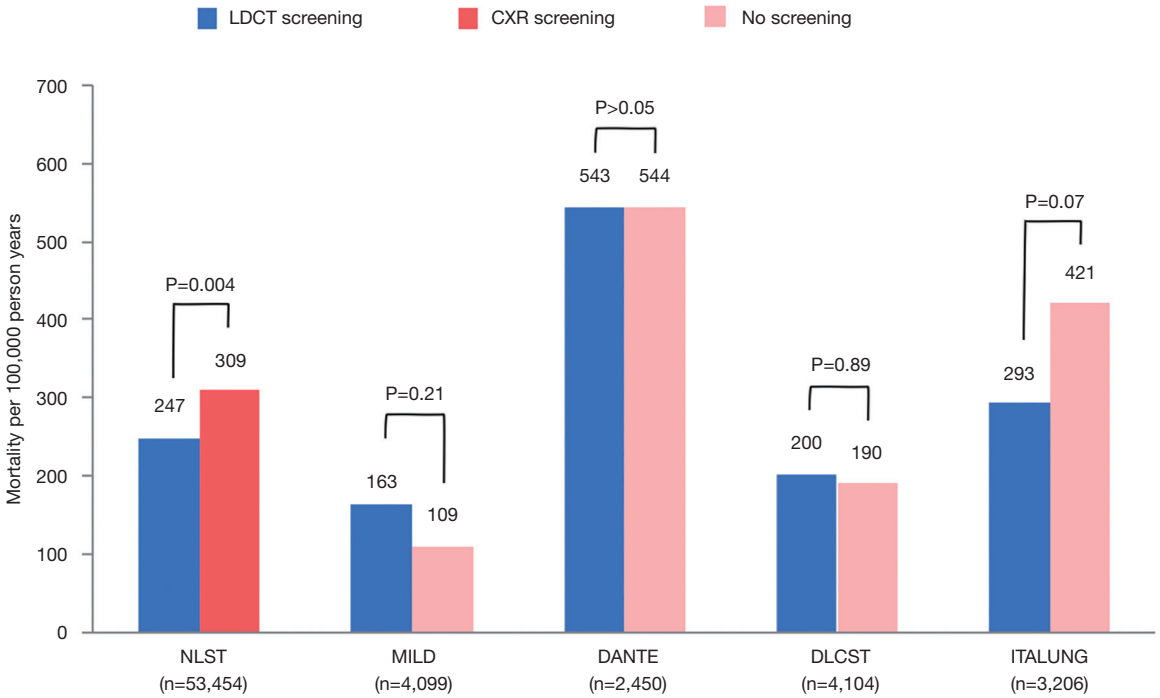

Figure 3 Mortality data reported by RCTs. LDCT, low-dose computed tomography; CXR, chest X-ray.

those diagnosed at later stages—in the United Kingdom, the one-year survival rate of stage I cancers has been estimated to be 72.5%, compared to 15.9% for stage IV cancers (55). Survival after VATS for lung cancer in Asia has been reported to be even higher (10,12,56). This increase in survival with earlier-stage cancers is expected because localized cancers can be effectively manged with localized treatment options with curative intent such as VATS and sublobar resection. Our finding that LDCT-detected cancers, compared to non-screened subjects, have a significantly higher proportion of earlier-stage cancers corresponds with the finding that LDCT-detected lung cancers also have a significantly higher resection rate, since surgery remains the treatment of choice for cancers and candidates fit for resection (57). Moreover, identification of earlier, smaller lesions usually means that screening-detected patients are more likely to be candidates for VATS and sublobar resection (7,11).

However, despite facilitating earlier diagnoses and more surgical resections of lung cancers, LDCT screening was only shown by two studies to lead to significantly decreased lung cancer-related mortality. There are two potential reasons to explain this result. Firstly, it is possible that a portion of screen-detected lung cancers might never be clinically significant or cause symptoms before the subject succumbs to other comorbid conditions, suggesting that a high proportion of LDCT-detected cancers in fact represents overdiagnoses. The NLST investigators have attempted to quantify the overdiagnosis rate of LDCT-detected lung cancers, and concluded that the probabilities that any LDCT-detected lung cancer, non-small cell lung cancer and bronchioalveolar lung cancer being an overdiagnosis are 18.5%, 22.5% and 78.9% respectively (58). The extent to which overdiagnosis contributes to the lack of significant decrease in lung cancer-related mortality remains to be determined, but a study estimates that the five-year overall survival for untreated stage I non-small cell lung cancer is only about 6% with a median survival of 9 months, indicating that most early stage lung cancers do require treatment to prolong survival (59). More research defining the radiological or histological features of comparatively indolent cancers and more conservative management of certain subsets of suspicious nodules, could help decrease the rate of unnecessary treatment for otherwise insignificant cancers.

A second reason to explain why not all studies showed a decrease in lung cancer-related mortality by LDCT screening is that the only two RCTs showing a significant

mortality decrease are also the ones with the largest sample sizes, with a combined sample size (n=69,276) almost five times that of all the other RCTs (n=13,859). Studies with larger sample sizes, or meta-analyses of data from existing trials, are likely needed to achieve sufficient power to detect the mortality benefit, if present, of LDCT screening. It is therefore likely that LDCT screening does improve lung cancer-related outcomes in some high-risk populations, despite smaller studies not concluding as such.

The rate of unnecessary invasive interventions in LDCT-screened subjects concluded by this review is low, at 0.07–1.9% (with most studies estimating the rate to be below 0.63%; *Table 2*). This rate of unnecessary interventions is comparable to other, more established screening programs such as mammography screening, which has been estimated to lead to unnecessary breast lesion biopsies in less than 0.66% of screened subjects (60). With this low rate of unnecessary invasive procedures and likelihood that LDCT screening improves lung cancer-related outcomes, multiple countries such as the United States, Canada and the United Kingdom are implementing LDCT lung cancer screening in their healthcare systems.

How applicable is the data from this review to populations outside the West? Both of the largest trials (NLST and NELSON) focused on smokers as the high-risk population for developing lung cancer, but data from these western studies may not be completely applicable to Asian patients, for example. Six of the newer trials included in this review were conducted in Asia, with a generally lower lung cancer diagnostic rate compared to western studies, suggesting that the appropriate target screening population has not yet been delineated among Asians. Focusing on patients of Chinese ethnicity, one of the major differences between lung cancer patients in Hong Kong and the west is that the proportion of non-smokers is higher in the former than the latter (30% *vs.* 10–15%) (61,62). Indeed, one of the reviewed Chinese studies found a borderline significantly higher lung cancer incidence rate among non-smokers compared to smokers, suggesting that non-smokers should also be included in screening programs of our population (19). Emerging studies are beginning to demonstrate possible biological differences between lung cancers in Asian and Western populations (63,64). More research should be conducted to delineate other significant risk factors for lung cancer in our locale, such as EGFR mutations, to define a more specific target screening population.

Even if LDCT screening led to improved lung cancer-related outcomes with minimal risks, the cost-effectiveness of such a program in our society must also be considered. A widely accepted calculation to assess an intervention's cost-effectiveness is the incremental cost-effectiveness ratio (ICER), which provides information on the net cost to achieve a unit of health, usually presented as life-years (LY) or quality-adjusted life-years (QALY) gained (65). There is no standardisation of ICER thresholds to inform decision making in Asia. In the United States, an arbitrary upper threshold of USD 50,000/QALY gained has traditionally been used to decide that an intervention is cost-effective (65), but health economists have recently proposed a higher cut-off of USD 100,000/QALY gained (66). In the United Kingdom, the National Institute for Health and Care Excellence (NICE) guidelines recommend an upper threshold of GBP 30,000 (USD 37,948)/QALY gained (67). According to a systematic review of cost-effectiveness studies of LDCT screening, the ICER for screening has been estimated to be USD 1,464 to 2,322,700 (68). Out of the nine reviewed studies, ICER calculated from seven studies is lower than USD 100,000/QALY gained and from five studies is lower than GBP 30,000/QALY gained, suggesting that LDCT screening could be cost-effective in most contexts. Using Hong Kong as an example, because the cost of a LDCT scan in Hong Kong (about USD 255) is lower than the cost reported and used for some western analyses (USD 1,130), the ICER for screening in Hong Kong could potentially be even lower than the currently available numbers, especially if the target screening population is more appropriately defined as suggested above. More locally relevant cost-effectiveness analyses should be conducted to define the health benefits of a LDCT lung cancer screening program in Asia.

Limitations and future directions

A major limitation of this literature review is the lack of consistency in the design of the individual studies included. Heterogeneity between the reviewed studies exists in terms of the screening population selection, screening intervals and study duration. For this reason, we have deliberately avoided performing a meta-analysis combining the studies' data. Less than half of the trials in the literature review are RCTs, which makes comparing LDCT screening with other forms of screening difficult. Finally, a full review of all the side effects of screening, such as increased radiation and psychological stress of LDCT false positives on the patient, is important to note before a screening program can be suggested, but was not done in this review.

Therefore, future research directions should include standardised and larger-scale randomised-controlled trials conducted in Asian populations, with a particular focus to delineate Asian-specific risk factors for lung cancer in order to properly target high-risk groups in our population. In addition, further studies to more appropriately define LDCT scan-positive lesions and determine scan features more specific to lung cancer, such as high lesion doubling time, can decrease the rate of unnecessary interventions.

Conclusions

LDCT screening is effective in diagnosing early-stage, resectable lung cancers, especially when compared to CXR screening or no screening. LDCT screening may also decrease lung cancer-related mortality with an acceptable rate of unnecessary interventions. Implementation of LDCT lung cancer screening in Chinese and other Asian populations can be considered after more locally relevant screening trials and cost-effectiveness analyses.

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Footnote

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